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Acute hypercalcemic hypertension in man: Role of hemodynamics, catecholamines, and renin

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Acute hypercalcemic hypertension in man: Role of hemodynamics, catecholamines, and renin. The effect of acute hypercalcemia on blood pressure, blood volume, hemodynamic parameters, plasma norepinephrine, epinephrine, dopamine, renin, and aldosterone concentrations was investigated. After 1 hour of equilibration, 10 patients received an infusion of calcium gluconate in 5% dextrose (calcium 15 mg/kg of body wt in 3 hours). The calcium infusion increased the mean serum calcium from 8.7 to 13.0 mg/dl, the systolic blood pressure from 144 ± 10 to 184 ± (SEM) 12 mm Hg ($P < 0.001$), the diastolic pressure from 78 ± 4 to 93 ± 5 mm Hg ($P < 0.01$). The plasma volume was decreased by 9% ($P < 0.001$), whereas the hematocrit was increased ($P < 0.05$). Heart rate and cardiac output remained unchanged. Total peripheral resistance was increased from 1643 ± 223 to 2256 ± 387 dyne·sec/cm^5 ($P < 0.05$). The plasma epinephrine concentration rose from 4.5 ± 0.7 to 6.9 ± 1.2 ng/dl ($P < 0.01$). The plasma norepinephrine concentration was unchanged after 2 hours and increased only slightly after 3 hours of calcium infusion. Plasma renin, aldosterone, and dopamine concentrations were not significantly changed. These findings demonstrate that acute hypercalcemic hypertension is mediated by an increase in peripheral vascular resistance. Hypercalcemic hypertension may be induced by a direct effect of calcium on blood vessels; calcium-mediated increase in adrenal epinephrine release may play a mild contributory role, and plasma volume contraction, an inhibitory role.

Hypertension hypercalcémique aiguë chez l'homme: Rôle des facteurs hémodynamiques, des catécholamines, et de la rénine plasmatiques. L'effet de l'hypercalcémie aiguë sur la pression artérielle, le volume sanguin, les paramètres hémodynamiques, la norépinéphrine, l'épinéphrine, la dopamine, la rénine, et l'aldostérone plasmatiques a été étudié. Après une heure d'équilibration, 10 sujets ont reçu une perfusion de gluconate de calcium dans du dextrose 5% (calcium, 15 mg/kg de poids en 3 heures). La perfusion de calcium a augmenté la concentration sérique moyenne de calcium de 8,7 à 13,0 mg/dl, la pression artérielle systolique de 144 ± 10 à 184 ± (SEM) 12 mm Hg ($P < 0,001$), la pression diastolique de 78 ± 4 à 93 ± 5 mm Hg ($P < 0,01$). Le volume plasmatique a diminué de 9% ($P < 0,001$) alors que l'hématocrite a augmenté ($P < 0,05$). La fréquence cardiaque et le débit cardiaque sont restés inchangés. Les résistances totales périphériques ont augmenté de 1643 ± 223 à 2256 ± 387 dyne·sec/cm^5 ($P < 0,05$). La concentration plasmatique de norépinéphrine n'était pas modifiée après 2 heures et n'a que peu augmenté après trois heures de perfusion de calcium. Les concentrations plasmatiques de rénine, d'aldostérone et de dopamine n'ont pas été significativement modifiées. Ces constatations montrent que l'hypertension aiguë hypercalcémique a pour médiateur une augmentation des résistances vasculaires périphériques. L'hypertension hypercalcémique peut être déterminée par un effet direct de calcium sur les vaisseaux; l'augmentation de la libération d'épinéphrine par les surrénales, qui a le calcium pour médiateur, peut jouer un rôle adjuvant faible et la contraction du volume plasmatique un rôle inhibiteur.

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Calcium is an important factor in the regulation of blood pressure. It plays a central role in the coupling between excitation and contraction of striated and vascular smooth muscle cells [1]. Moreover, variations in the concentration of calcium in the blood may be accompanied by parallel changes in blood pressure. A rapid reduction of serum calcium concentration induces hypotension in man [2, 3] and in the experimental animal [4]. Conversely, both acute [5, 6] or chronic forms of hypercalcemia [7–12] may be associated with hypertension. The mechanism by which excess calcium induces hypertension is still unclear. Theoretically, hypercalcemia could influence blood pressure by a direct action on the vascular muscle cells; or its cardiovascular effect could be mediated by other blood-pressure-regulating factors such as the renin-angiotensin-aldosterone axis, the sympathetic nervous system, and circulatory volume.

Plasma renin levels during acute hypercalcemia in man are unchanged or slightly decreased [6, 11, 12]. Only few data are available on the hemodynamic characteristics of hypercalcemic hypertension [13, 14]. Moreover, plasma and urinary catecholamines and blood volume have not been evaluated in this condition. Therefore, the present study was undertaken to investigate the role of plasma renin, aldosterone, and catecholamines levels, plasma and blood volume, and important hemodynamic parameters in the genesis of acute hypercalcemic hypertension in man.

Methods

Studies with calcium infusion. Because of our previous demonstration of pressor responses to acute hypercalcemia in subjects with or without various degrees of renal failure [6], we again asked subjects with normal or mildly impaired kidney function to participate in a study. During 1.5 years of recruitment in the outpatient and inpatient departments of our hospital, ten subjects, aged 19 to 71 years, volunteered and gave informed consent to undergo the investigations described below. They were six patients with normal kidney function (serum creatinine, < 1.3 mg/dl; ^{51}Cr-EDTA constant infusion clearance [15], > 95 ml/min·1.73 m^2) and four with slightly impaired kidney function (serum creatinine, 2.2 to 2.8 mg/dl; ^{51}Cr-EDTA constant infusion clearance, 24 to 36 ml/min·1.73 m^2). Diagnoses were chronic glomerulonephritis in four patients (biopsy-proven in three patients), and chronic interstitial nephritis ($N = 1$), pyelonephritis ($N = 1$), polycystic kidney disease ($N = 1$), unilateral renal cysts ($N = 1$) and unilateral renal hypoplasia (N

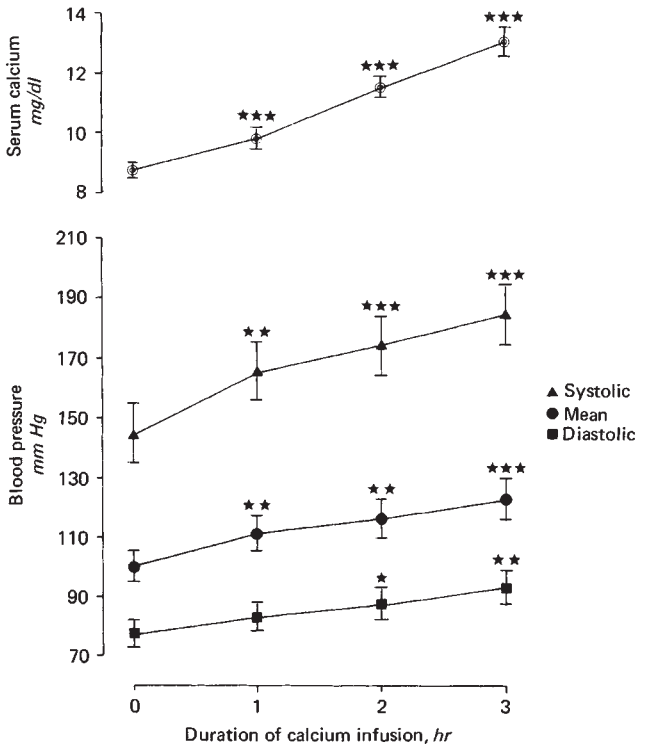

Fig. 1. *Serum calcium and blood pressure before and during i.v. calcium infusion.* Asterisks denote a significant difference from control conditions: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

= 1). An additional patient was evaluated following an episode of hematuria but symptoms had already disappeared and no cause was found. Blood pressure was normal (≤ 140/90 mm Hg) in eight patients and mildly elevated in two (diastolic 94 and 95 mm Hg, respectively). There was no history or evidence of stroke, heart failure, heart block, major arrhythmias, other cardiovascular complications, or extrarenal organ disease. Neither of the two female patients was on oral contraceptive drugs. Six patients agreed to participate in the entire procedure; the remaining four gave the consent for most of the procedure, except for the pulmonary artery catheterization and the measurement of cardiac output.

The study started at 8 A.M. The patients rested in the supine position. A microcatheter (Pulmocath) was inserted percutaneously, under local anesthesia, into an antecubital vein and floated under pressure monitoring to the pulmonary artery. A second catheter was introduced percutaneously into a brachial artery, for direct monitoring of arterial pressure. Both catheters served to collect blood samples for the assessment of cardiac output. In addition, an i.v. cannula was inserted in each arm; one was used to collect blood samples for various determinations, and the cannula on the contralateral arm was used for infusions. Following these preparatory steps, an i.v. infusion of 5% dextrose in water was started and maintained at a minimal rate (50 ml/hr) for 1 hour of equilibration. At the end of this equilibration period, basal measurements were obtained, and the dextrose infusion was replaced by an infusion of calcium gluconate in 5% dextrose solution. A total of 15 mg of calcium per kilogram of body weight, dissolved in 500 ml of dextrose solution, was infused for 3 hours. Heart rate and intraarterial pressure were monitored every 10 to 15 min throughout the entire procedure. Blood samples for determination of plasma calcium (by autoanalyzer), sodium, potassium (by flame photometer), phosphate (by colorimeter), protein (by the Biuret method), renin activity, aldosterone, norepinephrine, epinephrine, and dopamine levels were collected, and cardiac output (six patients) was measured immediately before and 2 and 3 hours after starting the calcium infusion. Blood and plasma volumes were determined by a radioisotope dilution technique using ^{131}I-albumin [16] before and at the end (3 hours) of the calcium infusion.

Studies with dextrose infusion. To evaluate possible calcium-independent influences of the infusion procedure on blood pressure, pulse rate, plasma volume, and endocrine parameters, three additional patients were studied. Their ages ranged between 58 and 73 years, and their serum creatinine concentrations, between 1.1 and 2.3 mg/dl (mean 1.7 ± 0.3 mg/dl). Following the 1-hour equilibration period (as above), these patients received an i.v. infusion of 500 ml of 5% dextrose without calcium; all measurements specified above were obtained except for cardiac output. Informed consent was obtained as in the former group of patients.

Special analytical procedures. Plasma renin activity and aldosterone were determined by radioimmunoassay [17, 18], and plasma norepinephrine, epinephrine and dopamine were determined by radioenzymatic assay [19], as reported previously from our laboratory [16, 20]. Intraarterial pressure was determined with a Statham P23 Db strain gauge transducer and registered on a Hellige three-channel ink recorder.

Cardiac output was determined by the Fick principle using oxygen saturation. Oxygen consumption was estimated with the tables of Fleisch [21]. Total peripheral resistance was calculated from cardiac output and intraarterial pressure.

Analysis of variance and (if a statistical significance was present) two-tailed Student's *t* test for paired data were used for the statistical comparison of values before and during the experimental procedure.

Results

Studies with calcium infusion. Calcium infusion increased serum calcium from 8.7 ± (SEM) 0.2 to 13.0 ± 0.5 mg/dl ($P < 0.001$); systolic blood pressure, from 144 ± 10 to 184 ± 12 mm Hg ($P < 0.001$); and diastolic blood pressure, from 78 ± 4 to 93 ± 5 mm Hg ($P < 0.01$) (Fig. 1). The hypertensive response was especially marked for systolic blood pressure, which was increased by more than 20 mm Hg in each patient. Diastolic and mean blood pressures were also consistently increased during calcium infusion. Pressor responses were comparable between subjects with normal or mildly impaired renal function (Δ mean blood pressure, +27 ± (SEM) 8 vs. +21 ± 4%), and no consistent difference was noted between subjects whose basal preinfusion blood pressure was normal (Δ diastolic blood pressure, +15 ± 4 mm Hg) or slightly increased (Δ diastolic blood pressure +5 and +20 mm Hg, respectively). Figure 2 illustrates the mean changes in blood pressure as related to the alterations in serum calcium. The increase in blood pressure became significant when serum calcium was increased by 1 to 2 mg/dl ($P < 0.05$).

Serum phosphorus was also increased during calcium infusion (from 2.6 ± 0.3 to 4.2 ± 0.3 mg/dl, $P < 0.001$). Plasma

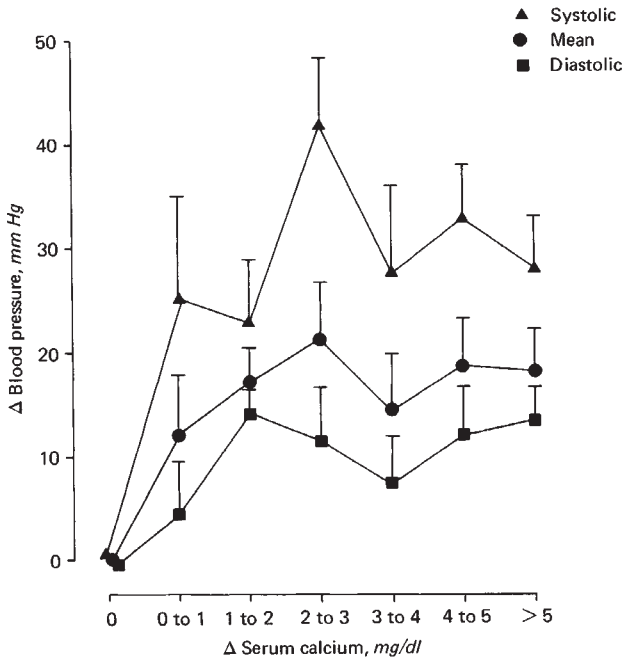

Fig. 2. *Relationship between changes in blood pressure and increments in serum calcium during i.v. calcium infusion.*

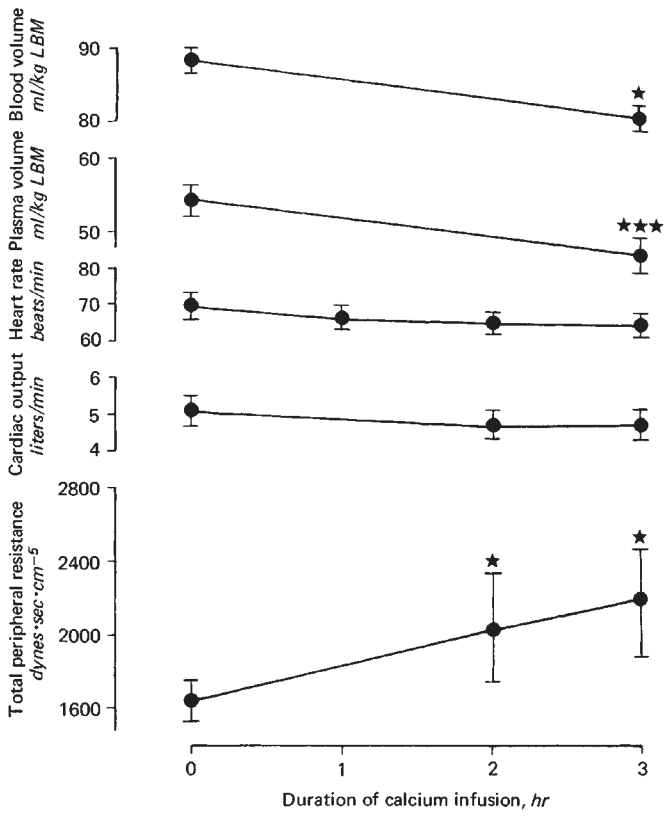

Fig. 3. *Plasma and blood volume and hemodynamic indices before and during calcium infusion.* Asterisks denote significant difference from control conditions: $*P < 0.05$; $***P < 0.001$.

sodium (138 ± 1 vs. 136 ± 2 mEq/liter) and potassium (3.8 ± 0.2 vs. 3.9 ± 0.1 mEq/liter) remained unchanged during calcium infusion.

During calcium infusion, blood volume decreased from 86.6 ± 1.8 to 81.5 ± 2.5 ml/kg of lean body mass (LBM) ($P < 0.05$) and plasma volume from 54.4 ± 2.5 to 49.5 ± 2.8 ml/kg of LBM ($P < 0.001$) (Fig. 3). Mean hematocrit was increased from 37.2 ± 2.4 to 39.4 ± 2.8% ($P < 0.05$), and total serum protein rose from 6.3 ± 0.2 to 6.7 ± 0.3 g/dl (not significant). Heart rate (69 ± 3 vs. 65 ± 3 beats/min) and cardiac output (5.0 ± 0.5 vs. 4.8 ± 0.5 liter/min) were not significantly changed, whereas total peripheral resistance was increased from 1643 ± 223 to 2256 ± 387 dyne·sec·cm^{-5} ($P < 0.05$).

Plasma epinephrine concentration increased progressively during calcium infusion; changes were significant both at 2 and 3 hours of infusion ($P < 0.05$ and $P < 0.01$, respectively) (Table 1). Plasma norepinephrine levels were unchanged after 2 hours of infusion, but a minimal although significant increase ($P < 0.05$) was noted after 3 hours. Plasma dopamine, renin, and aldosterone were not significantly altered. Calcium infusion was not associated with adverse symptoms; only one patient complained about fatigue 2 to 3 hours after the infusion.

Studies with dextrose infusion. In three subjects who received an i.v. infusion of dextrose only, blood pressure was 149/88 ± 12/5 mm Hg before the infusion and remained unchanged at 2 (143/88 ± 12/7 mm Hg) and 3 hours (143/88 ± 12/7 mm Hg) of infusion. Plasma epinephrine (4.4 ± 1.2 vs. 2.7 ± 1.1 vs. 4.2 ± 2.3 ng/dl), norepinephrine (31.8 ± 12.7 vs. 30.2 ± 15.5 vs. 34.8 ± 23.7 ng/dl), dopamine, renin activity, aldosterone, calcium, phosphorus, sodium, potassium, and protein levels, hematocrit, plasma and blood volume, as well as pulse rate, remained also unchanged during dextrose infusion.

Discussion

In this study the hemodynamic profile during acute elevation of serum calcium concentration (+4.3 mg/dl) was characterized by increases in blood pressure ($P < 0.001$) and total peripheral vascular resistance ($P < 0.05$), whereas cardiac output and

Table 1. Effect of acute hypercalcemia on plasma catecholamine, renin, and aldosterone levels[a]

Duration of calcium infusion, *hr*	Plasma epinephrine *ng/dl*	Plasma norepinephrine *ng/dl*	Plasma dopamine *ng/dl*	PRA *ng/ml/hr*	Plasma aldosterone *ng/dl*
0 (control)	4.5 ± 0.7	19.8 ± 4.3	11.6 ± 1.2	2.6 ± 0.8	6.1 ± 1.0
2	5.9 ± 1.1[b]	19.2 ± 3.9	12.4 ± 1.5	2.1 ± 0.7	6.9 ± 1.7
3	6.9 ± 1.2[c]	23.0 ± 4.6[b]	12.3 ± 1.3	1.9 ± 0.6	7.1 ± 1.9

[a] Values are the means ± SEM.
[b] $P < 0.05$, compared with values before calcium infusion.
[c] $P < 0.01$, compared with values before calcium infusion.

heart rate were unaltered. A similar observation was made in anesthetized dogs [22], and also described as a preliminary observation in one case [13]. It is known that calcium may increase the contractility of both the heart [14, 23] and the peripheral blood vessels [24, 25]. In previous studies in man, acute hypocalcemia was associated with a decreased cardiac output [26]; whereas calcium infusion was reported to cause an increased cardiac output [14] and a slowing of heart rate [23]. The latter studies differ from the present protocol in that the duration of calcium infusion was very short (5 to 6 min) and the degree of hypercalcemia milder, and no increase of blood pressure occurred in one of them [23]. Nevertheless, it appears possible that acute hypercalcemic hypertension is initiated by a very short phase with increased cardiac output [14] and rapidly progresses to a hemodynamic pattern with elevated peripheral vascular resistance. Moreover, because an increase in blood pressure induced by peripheral vasoconstriction should normally be associated with a compensatory decrease in cardiac output, the lack of the latter adaptive reaction in our patients may in fact indicate an inappropriately high cardiac output during acute hypercalcemia.

Calcium is essential for the contraction of striated and vascular smooth muscle cells. It is possible, therefore, that the cardiovascular changes that occur during hypercalcemia are at least partly owing to a direct effect of the cation of the vascular muscle cells [27]. It is equally possible that hypercalcemia increases the sensitivity of the cardiovascular system to the action of vasoconstrictor substances; but laboratory data do not support such a concept [25, 28].

The release of catecholamines is calcium dependent [29], and experimental data have suggested that increased calcium ion activity may augment the release of epinephrine from the adrenal medulla [30, 31] and of norepinephrine from the sympathetic nerve endings [32, 33]. Therefore, it appears possible that the increased plasma epinephrine concentrations during hypercalcemia in our patients were due to a direct stimulatory effect of calcium on adrenal medullary discharge. Plasma norepinephrine concentrations, which may be an approximate index of sympathetic nervous activity, remained unchanged after 2 hours of calcium infusion in these patients, but a minor increase was noted at 3 hours. The latter variation could be spontaneous or calcium dependent [32, 33]. It appears probable that the sympathetic system does not play a prime pathogenic role in acute hypercalcemic hypertension. Increases in plasma epinephrine during calcium infusion did not exceed the upper limit of the normal range [34]; and due to its high affinity to beta adrenergic receptors, an augmented release of this catecholamine would be expected to stimulate heart rate and cardiac output. The absence of "hyperkinetic circulatory pattern" following 2 to 3 hours of calcium infusion in our patients does not exclude a mild cardiac stimulatory effect of epinephrine, but its part in the mechanism of acute hypercalcemic hypertension may be contributory rather than dominant.

Because plasma renin levels were not significantly altered during calcium infusion, this factor could not account for acute hypercalcemic hypertension in our patients. Previous studies in man revealed unchanged [6, 11] or slightly decreased [12] levels of circulating renin following calcium infusion, as well as unaltered plasma renin activity during acute hypocalcemia [3]. Plasma aldosterone levels were also stable in our patients and in those of others [12]. An increase in circulating aldosterone following calcium infusion was described in patients with terminal renal failure [35], but in vitro studies revealed only an indirect relationship between calcium and aldosterone secretion [36].

The observed decrease in plasma volume ($P < 0.001$) and increase in hematocrit ($P < 0.05$) during acute hypercalcemia in our patients are consistent with a mild fluid loss from the vascular compartment, which cannot be explained by blood sampling. Volume contraction following calcium infusion could result from an extravascular shift secondary to a high blood pressure-induced increase in capillary filtration pressure, or from an augmented renal sodium diuresis [37]. Whatever the exact underlying mechanisms, it is possible that intravascular volume contraction may partly counteract the pressor mechanism of acute hypercalcemia in man.

Taken together, these findings suggest that acute hypercalcemic hypertension is mediated by an increase in peripheral vascular resistance. This hypertension may be induced by a direct effect of calcium on the cardiovascular system. A calcium-mediated increase in adrenal epinephrine release may play a contributory role; and a reduced plasma volume, an inhibitory role.

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